Cryopreserved saphenous vein allografts in infrainguinal revascularization: Analysis of 240 grafts

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Introduction: **Cryopreserved saphenous vein allografts (Cryograft; CryoLife, Kennesaw, Ga) have been used as conduit in infrainguinal revascularization when autogenous vein is inadequate or unavailable. Although some studies of Cryografts report poor long-term patency, an anticoagulation protocol may improve outcome. We evaluated our experience with Cryografts to further define their role in lower extremity revascularization.**

Patients and Methods: **Between March 1992 and March 2002, 240 infrainguinal revascularization procedures with Cryografts were performed in 199 limbs of 177 patients. Eighty-nine percent of procedures were performed because of ischemic rest pain or tissue loss, and 75% of vein grafts were implanted into infrapopliteal targets. Most patients received anticoagulation therapy with warfarin sodium or aspirin, or both, postoperatively. Mean age of the cohort was 78 years; 61% were women; 75% had hypertension, 58% had diabetes, and 38% had renal dysfunction; and 47% were current or past smokers.**

Results: **Mean follow-up was 7 months (range, 0-48 months). Primary patency rate was 83% at 1 month, 50% at 6 months, 30% at 12 months, and 18% at 24 months. Diabetes adversely affected graft patency. Warfarin sodium or antiplatelet therapy did not significantly improve graft patency. Limb salvage was 80% at 1 year and 71% at 2 years.**

Conclusions: **Cryografts have low primary patency rates that are not affected by anticoagulation with warfarin sodium. Short-term patency of these grafts may be sufficient to heal ischemic wounds and thereby prevent limb loss. However, other less expensive alternatives, eg, prosthetic grafts with vein cuffs, are available and appear to have better patency. Accordingly, use of Cryografts should be limited to revascularization through infected fields in patients without autogenous conduit. (J Vasc Surg 2003;38:15-21.)**

There is little doubt that autogenous greater saphenous vein is the preferred conduit for infrainguinal revascularization beyond the knee.[1,2] In the absence of autogenous greater saphenous vein, alternative autogenous conduits such as arm vein,[3] lesser saphenous vein,[4] and composite autogenous vein[5] have been used with good results. As a result of older patient age and the complexity of infrainguinal occlusive disease, adequate autogenous vein often is not available, and an alternative conduit must be found.

Although prosthetic grafts have been used successfully above the knee, they have been disappointing in infrageniculate bypass grafting.[6,7] Distal modification of prosthetic grafts with vein cuffs and distal arteriovenous fistulas has been shown to improve patency rates,[8-10] but is cumbersome. Human umbilical vein was used for a time, but has fallen out of favor because of late aneurysmal degeneration.[11] Composite sequential reconstructions have shown promise, but still require the presence of a segment of usable autogenous vein.[12]

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Competition of interest: none.

Presented at the Seventeenth Annual Meeting of the Western Vascular Society, Newport Beach, Calif, Sep 22-24, 2002.

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0741-5214/2003/$30.00 + 0
doi:10.1016/S0741-5214(03)00330-6

Given the absence of reliable conduit options for infrageniculate bypass grafting when suitable autogenous vein is unavailable, the feasibility of venous allografts has been studied.[13] Development[14] and standardization[15] of cryopreservation techniques have stimulated interest in the use of Cryografts (CryoLife, Kennesaw, Ga), which have the advantage of ease of handling and "off the shelf" availability. Although a number of clinical series using cryopreserved vein allografts have been published,[16-26] small sample size and contradictory findings have hampered their interpretation. Over the past decade we have extensively used Cryografts in infrainguinal revascularization, and herein report our results.

METHODS

We retrospectively evaluated all infrainguinal bypass procedures performed by the authors between March 1992 and March 2002 in which Cryografts were used. Office, hospital, and electronic charts were reviewed after institutional review board exemption status was granted. Epidemiology, indication for procedure, and graft anastomosis location were recorded. Comorbid conditions such as diabetes, hypertension, and current or past smoking were noted. Renal dysfunction was defined as serum creatinine concentration greater than 1.5 mg/dL or dialysis dependence (Table I).

All patients underwent preoperative arteriography. Vein mapping was routinely performed to outline and

Table I. Demographic data for 177 patients

Characteristic	*n*	*%*
Male	69	39
Female	108	61
Diabetes	102	58
Tobacco use	80	47
Hypertension	130	75
Renal dysfunction	66	38

define the size and quality of autogenous vein. The decision to use Cryograft as conduit was based on lack of autogenous vein, inadequate autogenous vein, or surgeon preference.

Cryografts were obtained at a cost of $4000 to $4500. They were kept frozen in solution containing dimethyl sulfoxide at −196°C until use. The Cryografts were seromatched for ABO/Rh blood grouping to the prospective recipients. They were then thawed, rinsed, and prepared according to the manufacturer's instructions. All Cryografts were 3.5 mm or greater in diameter.

In the operating room, proximal and target vessels were exposed, and 5000 U of heparin was administered before proximal clamp placement. Activated clotting time was measured and kept above 280 seconds. The Cryograft was reversed and placed in a superficial tunnel. The distal anastomosis was performed under tourniquet control. In 124 patients with 139 limbs (75%), warfarin sodium anticoagulation therapy was started within the first 2 postoperative days, with an international normalized ratio (INR) goal of 2.0-3.0. Therapeutic anticoagulation was achieved before discharge from the hospital. Warfarin therapy was modulated by the patients' internal medicine physicians and was continued until either graft failure or occurrence of an anticoagulation-related complication. Fifty patients with 58 limbs (32%) were given postoperative aspirin or clopidogrel. Thirty-seven patients with 42 limbs (21%) were discharged with both warfarin and antiplatelet therapy.

Perioperative and postoperative complications that occurred within 30 days of surgery were characterized as systemic or local.[27] Systemic complications included cardiac events (myocardial infarction or sustained atrial or ventricular arrhythmia), stroke, deep venous thrombosis, and pulmonary embolism. Local complications included wound infection, seroma, hemorrhage necessitating return to the operating room, and graft thrombosis within 24 hours. Thirty-day mortality was calculated.

A follow-up visit with the vascular surgeon was scheduled during the first month after discharge and 3 to 6 months thereafter. Duplex ultrasound scanning or angiography was ordered at the discretion of the vascular surgeon. During follow-up, Cryograft patency was assessed, in accordance with Society for Vascular Surgery standards, at physical examination performed by the vascular surgeon, who evaluated for presence of a palpable graft pulse or biphasic or triphasic Doppler waveform at two points over the superficially placed graft.[27] Suspected graft occlusion was verified at duplex scanning. Routine Cryograft duplex scanning was not performed during follow-up.

We defined two follow-up periods, one based on graft patency, as evaluated by a vascular surgeon or diagnostic test, and one based on limb salvage, as noted on office records or computerized dictated hospital reports. This was done because some patients were seen in the hospital by another physician after loss to follow-up with the vascular surgeon. Although graft patency could not be determined by any physician but a vascular surgeon, the presence or absence of the affected limb could be duly noted from any physician's dictated hospital report. Graft patency and limb salvage actuarial life tables were calculated. Follow-up for primary patency rate calculations ended when the graft was confirmed to be thrombosed or last known to be patent, whichever was shorter. Death and limb amputation were other end points for termination of patency. Follow-up for limb salvage rate calculation ended when the limb was amputated, the patient died, or the patient was last known to have the affected limb, on the basis of dictated reports from the electronic chart.

Graft patency and limb salvage rates at each time point for the 199 primary Cryografts were calculated with the life table method, as outlined by the Society of Vascular Surgery Ad Hoc Committee on Reporting Standards.[27] Mean values are reported, with standard error of the mean. All life table graphs shown have standard error less than 10%. The Cox multivariate regression model with forward selection was used to assess the influence on graft patency and limb salvage of gender, age less than 75 years, comorbid conditions (diabetes, smoking, hypertension, renal dysfunction), indication for surgery (rest pain, tissue loss), history of bypass grafting, and site of distal anastomosis (below-knee popliteal or tibial). Life table differences were analyzed with the log-rank test (Statistical Analysis System version 8.4; SAS, Cary, NC).

Patients. During the 10-year study 240 Cryografts were implanted into 199 limbs of 177 patients. This represents 19% of all infrainguinal bypass grafting performed by the authors during that period. Mean patient age at primary graft implantation was 78 years (range, 43-96 years). Demographic data for the 177 patients are shown in Table I. Fifty percent of the 199 limbs evaluated had not undergone previous infrainguinal bypass procedures; 27% had undergone one such procedure, and 21% had undergone two or more procedures. Eighty-nine percent of these procedures were performed because of tissue loss or rest pain (Fig 1). The common femoral artery was the most common site of inflow, and tibial vessels were the most common site of distal anastomosis (Table II).

One hundred twenty-seven additional procedures were performed after primary Cryograft placement (Fig 2). Thirty-five procedures were performed on failing Cryografts to maintain primary assisted patency; 17 procedures were performed on thrombosed grafts to restore secondary patency; and 75 new bypass grafts were placed after the primary Cryograft failed. Graft aneurysm rate was defined

by the number of aneurysms formed divided by the number of grafts patent.

RESULTS

Thirty-day mortality was 6%. In 7 of 11 patients who died within 30 days, death was secondary to a cardiac event. Overall morbidity for the 240 Cryograft revascularization procedures was 22%. Systemic complications included cardiac events (6%), pulmonary embolism (0.5%), deep venous thrombosis (0.5%), and stroke (0.5%). Local complications included wound infection (5%), seroma (1%), hemorrhage that necessitated return to the operating room (3%), and graft thrombosis within 24 hours (5%). Seventy-two percent of patients were alive at 1 year, and 69% of patients were alive at 2 years.

Follow-up to assess mean graft patency of the 199 primary grafts was at 7 ± 1 month. The primary patency rate for the cohort was 83% at 1 month, 50% at 6 months, 30% at 12 months, and 18% at 24 months (Fig 3). The primary patency of Cryografts to below-knee popliteal targets was 87% at 1 month and 61% at 6 months. Primary patency for Cryografts to infrapopliteal target vessels was 81% at 1 month, 49% at 6 months, 26% at 12 months, and 15% at 24 months (Fig 4). There was no statistically significant difference between below-knee and infrapopliteal Cryograft primary patency rates.

Thirty-one procedures were performed on 25 failing primary grafts to maintain primary assisted patency, which was 84% at 1 month, 53% at 6 months, 32% at 12 months, and 22% at 2 years. Fifteen procedures were performed on 14 thrombosed grafts to maintain secondary patency, which was 83% at 1 month, 52% at 6 months, 30% at 12 months, and 20% at 24 months. The difference between primary, primary assisted, and secondary patency rates was not statistically significant (log-rank test). At multivariate analysis, diabetes was the only factor independently associated with worse primary patency ($P < .02$; Cox regression analysis; Fig 5). Warfarin sodium, antiplatelet agent, or a combination of the two, did not have a statistically significant effect on primary graft patency in any treatment group (log-rank test).

In nine primary Cryografts aneurysmal degeneration developed, and all were repaired with interposition grafts. Mean time to aneurysm diagnosis was 21 ± 5 months (range, 4-46 months). Because of low graft patency at 2 years, aneurysmal degeneration rate was high at 44%. Two graft aneurysms ruptured, necessitating emergent repair.

Mean limb salvage follow-up was 14 ± 1 months. Limb salvage rate was 93% at 1 month, 88% at 6 months, 80% at 12 months, and 71% at 24 months (Fig 6). Multivariate analysis revealed that limb salvage rate was higher in limbs that underwent femoral to below-knee popliteal bypass grafting, as compared with those with femoral to infrapopliteal bypass grafts. This difference was statistically significant ($P = .054$, Cox regression analysis; $P < .05$, log-rank test; Fig 7).

The primary patency rate for the 41 secondary Cryografts was 85% at 1 month, 54% at 6 months, 17% at 12 months, and 8% at 24 months. Limb salvage rates for those limbs that received a secondary Cryograft or autogenous bypass graft was 100% at 6 months and 95% at 1 year. Within the first year the limb salvage rate was better in patients who received a secondary Cryograft or autogenous vein graft. However, this trend was not statistically significant (log-rank test).

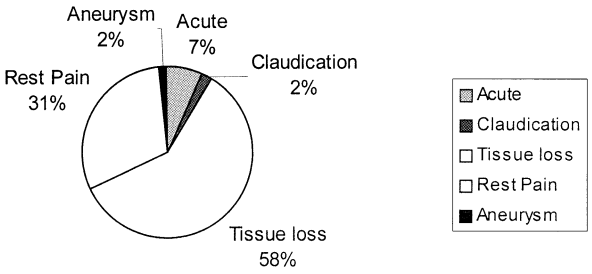

Fig 1. Indications for 199 primary revascularization procedures with Cryografts.

DISCUSSION

This study represents the largest reported experience with Cryografts. Use of Cryografts is attractive. The conduit is available "off the shelf" and has the physical appearance and handling of autogenous saphenous vein. Furthermore, its use foregoes the time and effort necessary to harvest and splice segments of alternative autogenous vein. It has potential to be the vascular surgeon's "dream conduit."

Initially, we used Cryografts not only when autogenous saphenous vein was unavailable or inadequate, but also in lieu of alternative autogenous vein. This explains in part our high percentage (50%) of limbs without previous bypass procedures. Over time, problems with Cryografts emerged, and our initial enthusiasm was replaced with cautious pragmatism. The purpose of this report is to evaluate our extensive experience with Cryografts and determine their role in the armamentarium of today's vascular surgeon.

Our cohort of 177 patients differs from that in other published studies of infrainguinal bypass grafting. With a mean age of 78 years, our patients were older than those in other large series.[1-3,5,10,12,22] The preponderance of women, 61% of our patients, also separates our group from other studies. More than a third of our patients had substantial renal dysfunction. Finally, the cumulative 1-year survival rate in our cohort was only 72%, which is lower than that reported in other series.[3,7] Our group of patients clearly falls into the more terminally ill portion of the spectrum, and this likely explains our relatively high 30-day mortality rate of 6%.

Evaluation of these grafts reveals poor 1-year primary patency of 30%; however, this result is similar to the 37% 1-year patency rate reported by Martin et al.[22] in the largest published series of Cryografts (Table III). Although others have reported higher Cryograft primary patency rates, interpretation of those results must be tempered by the small

Table II. Site of proximal and distal anastomosis in 199 primary cryograft revascularization procedures

	Proximal anastomosis													
	EIA		*CFA*		*SFA*		*PFA*		*AKP*		*PRG*		*Total*	
Distal anastomosis	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
AKP	0		0		1		0		0		0		1	.05
BKP	5		22		3		0		0		11		41	21
Tibial	9		77		17		2		1		21		127	64
TPT	0		2		0		0		0		1		3	2
Pedal	0		7		7		0		2		2		18	9
PRG	2		3		1		1		0		2		9	4
Total	16	8	111	56	29	15	3	1	3	1	37	19	199	100

EIA, External iliac artery; *CFA,* common femoral artery; *SFA,* superficial femoral artery; *PFA,* profunda femoral artery; *AKP,* above-knee popliteal artery; *BKP,* below-knee popliteal artery; *PRG,* previous graft; *Tibial,* anterior tibial, posterior tibial, peroneal arteries; *TPT,* tibioperoneal trunk.

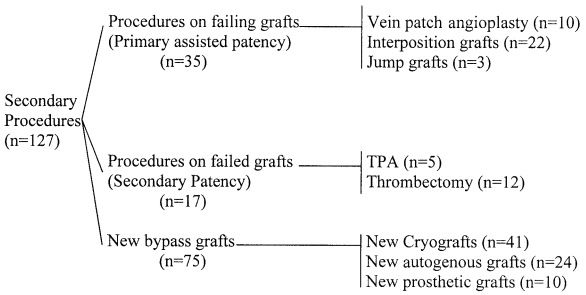

Fig 2. Categorization of 127 secondary procedures after primary revascularization with Cryografts. *TPA,* Tissue plasminogen activator.

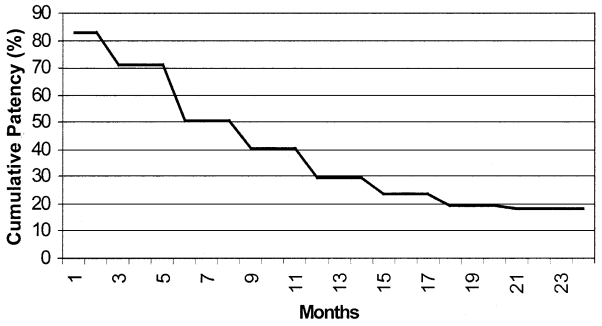

Fig 3. Primary patency curve and life table for 199 primary revascularization procedures with Cryografts.

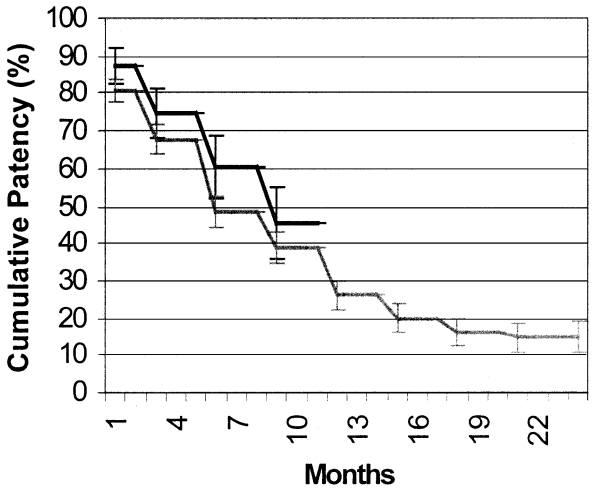

Fig 4. Comparison of primary patency rates in grafts with below-knee popliteal *(black line)* and infrapopliteal *(gray line)* distal anastomosis (P = NS; Cox multivariate regression analysis).

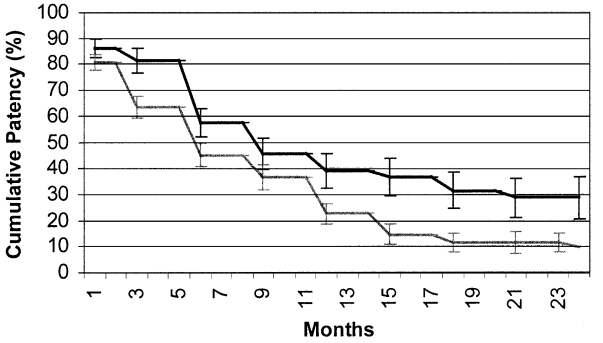

Fig 5. Effect of diabetes on primary Cryograft patency ($P < .05$; log-rank test). *Gray line,* Diabetes; *black line,* no diabetes.

number of grafts evaluated.[18,25] Our 1-year primary patency rate for Cryografts to infrapopliteal target vessels of 26% (Fig 4) is in the 21% to 48% primary patency rate reported for polytetrafluoroethylene (PTFE) grafts used in infrapopliteal position.[6,7] Furthermore, it is significantly less than the primary patency rate of 82% reported for infrapopliteal PTFE grafts modified with distal interposition vein cuffs.[9]

In a prospective trial of Cryografts in 24 patients, Buckley et al[16] reported an impressive 87% 1- year primary patency rate. These results are attributed to an anticoagulation protocol consisting of preoperative aspirin, perioperative low-dose heparin and dextran, and postoperative warfarin, aspirin, and dipyridamole. Of note, 42% of grafts in that series had distal anastamotic modification with either

vein cuffs or arteriovenous fistulas. In our series, 75% of patients were given warfarin sodium and 32% were given an antiplatelet agent; 21% of patients received both warfarin and antiplatelet therapy. Warfarin or antiplatelet therapy did not have a statistically significant effect on Cryograft patency in our series or other series.[17,20,22,26] In our series, administration of both warfarin and antiplatelet therapy did not improve graft patency. This finding differs from the high Cryograft patency rate achieved with combination therapy with warfarin sodium and aspirin in the prospective series by Buckley et al.[16] A limitation of our study is that the exact degree of anticoagulation over follow-up is not known for each individual patient; however, this limitation is present in most other retrospective Cryograft series.[19-22,25,26]

Although early graft failure in autogenous and prosthetic reconstruction procedures is usually due to myointimal hyperplasia, most Cryograft failures are due to allograft rejection.[17,28] Even though this has not been assessed in our study, allograft rejection involving both cell-mediated and humoral immune response has a role in graft failure.[17,28] The result is irreversible endothelial loss and progressive medial fibrosis and degeneration.[15] There is some controversy regarding the effect of the cryopreservation process itself on endothelial layer integrity. Nevertheless, there is evidence that the overall anatomy and fibrinolytic capacity of appropriately cryopreserved veins is maintained.[15]

Attempts to diminish the allograft rejection process in Cryografts with immunosuppression therapy had some success in a canine model.[29] However, use of azathioprine in a clinical trial was not successful.[16] Other immunosuppressive protocols may be effective; however, potential serious side effects of therapy may not justify clinical trials in this patient population. Although anticoagulation protocols may, in theory, improve Cryograft patency, it is unlikely that their effect alone is significant in the setting of allograft rejection that affects most of these grafts.

Secondary procedures for failing or failed Cryografts were uncommon in our group, and their success rate was low; primary assisted and secondary patency rates did not significantly differ from primary patency rates. The poor primary assisted patency rate explains our practice of not following up with routine duplex scanning. Our findings with regard to primary assisted patency and secondary patency are consistent with results reported by Martin et al,[22] but vary with findings of Walker et al.[26] In the latter series, the authors took an aggressive posture toward Cryograft thrombectomy and revision. Although almost half of their grafts could not be reopened, they were able to increase their 1-year cumulative secondary patency rate from 28% to 46%.

At logistic regression analysis only diabetes negatively affected Cryograft patency (Fig 5). Although previous bypass procedures[25] influence Cryograft patency rates, diabetes has not been previously reported to do so. There are conflicting reports that diabetes negatively[30] and positively[1,31] affects infrainguinal autogenous vein bypass patency.

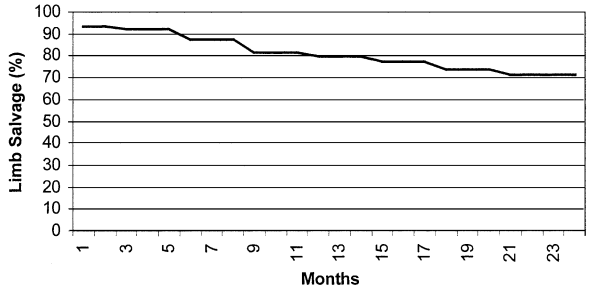

Fig 6. Limb salvage curve and life table for 199 limbs after primary Cryograft revascularization.

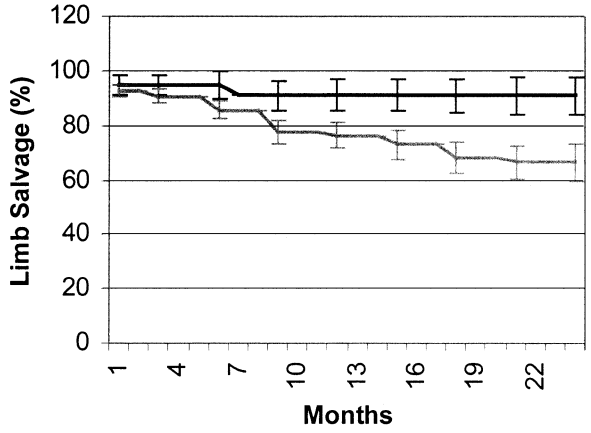

Fig 7. Effect of below-knee popliteal *(black line)* and infrapopliteal *(gray line)* distal Cryograft anastamosis on limb salvage ($P < .05$; log-rank test).

Cryografts that remain open for a prolonged period are prone to aneurysmal degeneration. In our series, aneurysmal degeneration developed in 9 grafts, for a 2-year aneurysm incidence of 44%. In the series by Martin et al,[22] aneurysmal degeneration developed 6 of 115 Cryografts, for an approximately 25% aneurysm formation rate at 2½ years. Aneurysmal degeneration affects other biologic grafts, and has been reported in 33% of human umbilical vein grafts at 2 years.[11]

Despite low Cryograft patency, limb salvage in our group of patients was 71% at 2 years, similar to the results reported by Martin et al[22] and Harris et al[19] (Table III). Our relatively high limb salvage rate in the face of low graft patency can be explained in part by the 41 secondary Cryografts and 24 secondary autogenous grafts that were placed after primary Cryograft failure. There was a trend toward a higher limb salvage rate in patients who underwent secondary bypass procedures, although it fell short of statistical significance. Repetitive bypass grafting significantly extends limb salvage.[32] Another possibility to explain our high limb salvage rate is that Cryografts, while patent, enabled healing of lower extremity ulcerations in a large proportion of our patients. Ulcers may not have

Table III. Published Cryograft series with more than 20 patients

Author	*Number of grafts*	*Primary patency at 1 year (%)*	*Secondary patency at 1 year (%)*	*Limb salvage at 2 years (%)*
Buckley et al[16]	26	87	NR	80
Carpenter & Tomaszewski[17]	40	13	NR	42*
Harris et al[19]	80	36.8	NR	62.3†
Harris et al[20]	25	NR	36	74*
Leseche et al[21]	25	NR	52	78
Martin et al[22]	115	37	40	66‡
Shah et al[25]	43	66	NR	NR
Walker et al[26]	39	28	46	67‡

NR, Not reported.
*At 12 months.
†At 3 years.
‡At last follow-up.

recurred despite graft failure. This hypothesis cannot be proved in our series or in any study that does not prospectively surveil ulcer healing along with limb salvage. Limb salvage in excess of graft patency has been described in PTFE grafts[6] and human umbilical artery grafts.[11]

Duration and completeness of follow-up are admitted weaknesses of this study. Mean follow-up for graft patency of 7 months and for limb salvage of 11 months is relatively short; however, it is within the follow-up range of 5 to 21 months reported in other Cryograft series.[18,20,22-26] We propose several reasons to explain our relatively high patient loss to follow-up. With mean age of 78 years, our patient cohort was older than patients in many other studies. Many of these patients were not in independent living situations, and because of social and economic reasons they could not comply with follow-up. Furthermore, given our tertiary care setting, many of our patients were referred from communities outside our metropolitan area; these patients returned to their local communities for follow-up.

Our decade-long experience with Cryografts has taught us some important lessons. Although Cryografts look, feel, and handle like autogenous vein, they are far from being the holy grail of infrainguinal reconstruction. Despite an acceptable early primary graft patency rate, Cryografts have poor midterm patency. Primary patency is worse in patients with diabetes, and is not significantly affected by warfarin therapy. Although we do not negate the excellent results noted by Buckley et al,[16] who used an extensive anticoagulation protocol, given the immunologic mechanism of Cryograft failure, we are skeptical that anticoagulation alone is sufficient to prevent graft occlusion. Those grafts that do remain open for extended periods have a significant rate of aneurysm formation. Secondary procedures on failing or failed grafts do not provide significantly improved patency. Cryografts may affect definitive ulcer healing despite early occlusion. In addition, a policy of repetitive Cryograft bypass grafting may enable improved limb salvage. However, similar or better results may be obtained with a more cost-effective conduit, eg, PTFE grafts, with or without distal graft modification. All of these issues have been recently overshadowed by the US Food and Drug Administration order to retain all Cryografts processed by Cryolife, a major supplier of the grafts, because of concern about infectious disease prevention procedures.[33]

We have significantly narrowed our indications for Cryograft use. Cryografts may be justified in revascularization procedures through infected fields when autogenous conduit is not available or adequate. In that clinical setting, use of this graft is adequate.[18] Otherwise, PTFE grafts should be considered for use in this difficult patient population.

We thank Meenu Sandhu, MS, of the Department of Biostatistics, Cedars-Sinai Medical Center, for assistance with statistical analysis.

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Submitted Sep 30, 2002; accepted Feb 12, 2003.